Laughing gas in pediatric emergency department-fun for all participants: Vitamin B12 status among medical staff working with nitrous oxide

Staubli, G ; Baumgartner, M R ; Sass, J O ; Hersberger, M

Abstract: The efficiency of nitrous oxide in an equimolar mixture with oxygen or in concentrations up to 70% is approved for short painful procedures. Evaluation of the vitamin B12 levels in anesthetic staff applying nitrous oxide showed reduced vitamin B12 plasma levels. This study examines the vitamin B12 status of medical staff working with nitrous oxide in a pediatric emergency department (ED). Medical staff of the ED at the University Children's Hospital Zurich participated. The vitamin B12 status was evaluated by measuring homocysteine, methylmalonic acid, vitamin B12, blood count, and theMTHFR C677T genotype. As a control group, medical personnel working in the "nitrous oxide–free" pediatric intensive care unit were recruited. were recruited.

DOI: https://doi.org/10.1097/PEC.0000000000000582

Laughing Gas in a Pediatric Emergency Department—Fun for All Participants

Vitamin B_{12} Status Among Medical Staff Working With Nitrous Oxide

Georg Staubli, MD, Matthias Baumgartner, MD,† Jörn Oliver Sass, PhD,‡ and Martin Hersberger, PhD‡*

The efficiency of nitrous oxide in an equimolar mixture with oxygen or in concentrations up to 70% is approved for short painful procedures. Evaluation of the vitamin B_{12} levels in anesthetic staff applying nitrous oxide showed reduced vitamin B_{12} plasma levels. This study examines the vitamin B_{12} status of medical staff working with nitrous oxide in a pediatric emergency department (ED). Medical staff of the ED at the University Children's Hospital Zurich participated. The vitamin B_{12} status was evaluated by measuring homocysteine, methylmalonic acid, vitamin B_{12}, blood count, and the MTHFR C677T genotype. As a control group, medical personnel working in the "nitrous oxide–free" pediatric intensive care unit were recruited.

Results: The parameters for the vitamin B_{12} status of all participants were in the reference range, and there were no significant differences for the 2 groups. By trend, the ED staff showed higher vitamin B_{12} levels. The ED staff members were slightly older ($P = 0.07$) and had higher hemoglobin levels ($P < 0.04$) compared with the pediatric intensive care unit staff.

Conclusions: The use of nitrous oxide (50%-70%) with a demand valve is safe for the vitamin B_{12} status of medical personnel in the ED.

Key Words: nitrous oxide, vitamin B_{12}, safety

(*Pediatr Emer Care* 2015;00: 00–00)

The use of nitrous oxide in an equimolar mixture with oxygen or at a concentration up to 70% is a very efficient and safe method for analgosedation for children.[1–3] The safety profile is very high if applied in an adequate manner, and severe adverse effects are very rare.[4,5] In the setting of an emergency department (ED), nitrous oxide is used for short painful procedures for analgosedation and is not comparable with its use in anesthetics. In 2003, we established the equimolar mixture with demand valve at our ED. In 2005, we additionally introduced a system with a blender that allows to increase the nitrous oxide concentration up to 70%. The higher concentration of nitrous oxide with its greater analgesic and sedative effect allows to perform procedures that are more painful.[2]

Measurements of nitrous oxide concentrations in the room air of our emergency cubicles during the use of equimolar nitrous oxide mixture confirmed that the concentrations did not exceed the legal limits—neither the long-term maximum workplace concentration (MAC) value of 200 ppm during 8 h/d nor the short-term MAC of 800 ppm during 15 min/d. Despite of these measurements, we could not assure the safety for our personnel regarding their vitamin B_{12} metabolism. Indeed, there is indication that nitrous oxide will bind cobalamin I irreversibly,[6] and some older studies showed that medical staff working in operation rooms have reduced vitamin B_{12} levels although not of clinical relevance.[7–9] The influence of regular use of nitrous oxide in an ED setting on vitamin B_{12} metabolism was analyzed for individuals working in an ED by Ekbom et al.[10] Ekbom et al examined the blood samples of 2 nurses applying nitrous oxide for short painful procedures before and after an intervention. They had no signs of hyperhomocysteinemia or macrocytosis.

There is no study that has examined this in a whole ED team using the nitrous oxide for short, painful procedures. The aim of this study was thus to examine the vitamin B_{12} status of medical staff working routinely with nitrous oxide using a demand valve for short painful procedures in a pediatric ED.

METHODS

Study Design and Settings

This is a cross-sectional study with a control group in a tertiary hospital, the University Children's Hospital Zurich. The hospital is situated in a metropolitan area with about 450,000 habitants, but it is also the tertiary hospital for the neighboring rural region with approximately 1.2 million people. More than 37,000 pediatric patients younger than 16 years are treated in the interdisciplinary ED. The physicians are residents that are supervised by pediatric emergency physicians. The nurses and physicians are working exclusively at the ED. The study was approved by the local ethics committee.

Participants

All medical staff members (nurses, registrars, pediatric emergency physicians) that had been working more than 1 year at the interdisciplinary ED of the University Children's Hospital Zurich were asked to participate in this study. Of the 7 physicians, 5 worked full time and 2 part time, but all more than 8 shifts per month. Of the 22 nurses, 10 worked full time and 12 worked part time. As for the control group, we chose the same number of medical personnel working in the pediatric intensive care unit (PICU) in the same hospital assuming the same level of work strain. The PICU is a nitrous oxide–free department.

At our ED, we use nitrous oxide either as equimolar mixture with demand valve or with the system with a blender that allows to increase the nitrous oxide concentration up to 70%. With this mixture, the exhaled air is lead into the room air. The system with the blender is fixed in our procedure room and connected to the wall suction. Emission of nitrous oxide with this system happens only by incorrect use or if the child is not cooperative. At our interdisciplinary ED, we use nitrous oxide for short painful procedures up to 30 minutes.

We apply nitrous oxide in 2% to 3% of our 37,000 pediatric patients per year. The main indications are lumbar punctures, laceration repair, treatment of fractures, and luxations. Most of these procedures are performed in our procedure room with the blender. In contrast, the equimolar mixture is mobile and therefore used for

From the *Department of Emergency Care, †Divisions of Metabolism, ‡Clinical Chemistry and Biochemistry, University Children's Hospital and Children's Research Center, Zurich, Switzerland.

Disclosure: The authors declare no conflict of interest.

Reprints: Georg Staubli, MD, Department of Emergency, University Children's Hospital and Children's Research Center, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland (e-mail: georg.staubli@kispi.uzh.ch).

ISSN: 0749-5161

procedures in all our emergency cubicles. After the information of the patient and its parents, the nurse usually starts the inhalation with nitrous oxide, and the treating doctor starts the procedure 3 to 5 minutes later.

All medical staff members (nurses, consultants) that had been working for more than 1 year at the interdisciplinary ED of the University Children's Hospital Zurich were asked to participate in this study.

Exclusion criteria for this study were as follows: working less than 1 year in the emergency department (ED), resection of stomach or guts, pregnancy in the second or third trimester, no written informed consent, and vegan diet.

Written informed consent was obtained from all participants, and a venous blood draw was performed to determine their vitamin B_{12} status. We analyzed vitamin B_{12} on an Elecsys 2010 (Roche, Rotkreuz, Switzerland), homocysteine on a DxC600 (Beckmann Coulter, Nyon, Switzerland), methylmalonic acid (MMA) by liquid chromatography/mass spectrometry on a SCIEX QTrap 4000 LC/MS/MS System (AB Sciex GmbH, Brugg, Switzerland), blood count on a XN-1000 hematology analyzer (Sysmex AG, Horgen, Switzerland), and the common MTHFR polymorphism c.C677T by fluorescence resonance energy transfer on a LighCycler2.0 (Roche). All the analyses were done in accredited medical laboratories of the University Children's Hospital Zurich.

Exploratory statistics were performed using the Statistical Package for the Social Sciences (SPSS-X). The results are expressed as mean ± SEM. Analysis of covariance with age as covariance was used for comparison of means. Pearson χ^2 test was used to compare frequency distributions.

P values less than 0.05 are considered significant.

RESULTS

All of the 31 staff members working in the ED for more than 1 year participated in the study with the exception of 2 nurses: one refused to sign the written informed consent, and the other met the exclusion criteria of the study. The remaining 29 participants were composed of 7 pediatric emergency physicians and 22 nurses. Five physicians worked full time, 2 worked part time, but all more than 50% (2.5 shifts per week). Ten nurses worked full time, and 12 worked part time. We estimated that each physician attended on average 185 analgosedations a year, and each nurse performed an average of 39 analgosedations a year. In the PICU, the control group were 5 physicians and 26 nurses included.

Comparing the characteristics between the ED and the PICU groups, we observed that the ED personnel is older than the PICU personnel with a mean of 41.3 versus 34.6 years ($P = 0.007$), whereas there was no difference in the distribution for sex ($P = 0.42$).

Looking at the individual means of the parameters reflecting the vitamin B_{12} status (Table 1), we observed that all means of the investigated parameters are in the reference range for adults and that there is no difference between the 2 groups. There were results out of the reference ranges in both groups. For vitamin B_{12} (reference range, 191-663 ng/L), 5 participants in the ER group (lowest value, 170 ng/L) and 2 participants in the PICU group (lowest value, 118 ng/L) had lower values. There was only a nonsignificant trend for higher vitamin B_{12} levels in ED members (339 vs 309 ng/L).

For homocysteine (reference range, 5-15 mmol/L), only 1 participant from the ER group had a value of 16.4 mmol/L but with normal vitamin B_{12} level and normal MMA level. For the MMA (reference range, 70-300 mmol/L), 3 participants in the ER group (highest value, 561 mmol/L) and 5 participants in the PICU group (highest value, 521 mmol/L) had values above the reference range.

No anemia was present in any of the participants according to the blood count. However, ED personnel had higher hemoglobin values (138 vs 132 g/L) even if corrected for age and sex. One participant of the PICU group had thrombopenia.

We also determined the polymorphism c.C677T for the MTHFR enzyme that could confound plasma levels of homocysteine in the homozygous state.[11] Although 3 volunteers in the ED and 2 in the PICU group are carriers of a homozygous mutation, none of these volunteers had increased homocysteine plasma levels, excluding the potential confounding effect of the MTHFR polymorphism.

DISCUSSION

The application of nitrous oxide, either in an equimolar mixture with air or in a concentration up to 70%, with a demand valve for short, painful procedures, is one of the most important

TABLE 1. Vitamin B_{12} Status of the Participants

	ED (n = 29)		PICU (n = 31)			
Variable	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**	**F**	***P****
Vitamin B_{12}, ng/L	339.47 (161.88)	281.18–396.25	309.55 (113.79)	270.85–354.50	0.05	0.82
Homocysteine, μmol/L	9.25 (2.51)	8.40–10.20	9.30 (1.99)	8.65–10.01	0.04	0.85
Methyl malonic acid, μmol/L	215.17 (109.62)	178.55–261.07	176.89 (95.87)	145.56–212.61	2.79	0.10
MTHFR c.C677T	1.66 (0.67)	1.43–1.90	1.52 (0.62)	1.31–1.75	0.39	0.54
Hemoglobin, g/L	138.62 (8.37)	135.79–141.68	132.16 (11.93)	128.21–136.15	4.45	**0.04**†
Hematocrit, %	0.42 (0.10)	0.39–0.46	0.38 (0.03)	0.37–0.39	6.48	0.14
Erythrocytes, $\times 10^{12}$/L	4.62 (0.28)	4.52–4.73	4.52 (0.32)	4.40–4.64	1.80	0.19
MCV, fl	86.52 (3.10)	85.44–87.67	84.97 (5.05)	83.03–86.56	0.66	0.42
MCH, pg	30.10 (1.08)	29.73–30.47	29.35 (2.21)	28.50–30.07	1.43	0.24
MCHC, g/L	347.66 (7.64)	345.04–350.58	344.52 (11.46)	340.41–348.21	1.62	0.21
Platelet count, $\times 10^9$/L	268.79 (50.66)	250.83–285.71	267.45 (60.26)	245.41–287.72	0.53	0.47
Leucocytes, $\times 10^9$/L	7.04 (1.68)	6.42–7.64	6.95 (1.31)	6.48–7.42	1.02	0.32

*Analyses of covariance controlled for age.

†Significant, also if additionally controlled for sex ($P = 0.044$).

CI indicates confidence interval; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

methods for analgosedation at our pediatric ED. In this study, we examined practically all long-standing staff members at our ED regarding their vitamin B_{12} metabolism. We could show that the mean values of all relevant parameters that determine normal functioning of vitamin B_{12} metabolism in the applying personnel are within the reference range. We have to state that, of 29 ED and 31 PICU members serving as control group, 5 ED and 2 PICU members, respectively, had reduced total vitamin B_{12} level than the selected lower range of 191 ng/L. None of these, however, showed an increase in homocysteine and MMA levels in plasma, suggesting that there was no functional vitamin B_{12} deficiency present. Indeed, the mean vitamin B_{12} levels of ED personnel were higher than in PICU personnel. Notably, the lack of a statistical significant difference could be related to our small sample size that reduced the power of this study.

Our study confirms the results of the study of Ekbom et al, who also showed that 2 nurses applying nitrous oxide in the ED had normal parameters regarding their vitamin B_{12} metabolism.

The normal vitamin B_{12} metabolism in the applying personnel argues that the use of demand valve devices to deliver nitrous oxide to children and adolescents for short analgosedation in the ED setting is safe for the applying personnel. The use of nitrous oxide in the ED setting for short painful procedures for analgosedation is not comparable with the use of nitrous oxide in the anesthetic setting for general anesthesia. The exposure to nitrous oxide of ED staff is very short and only a few times per day, whereas in the anesthetic setting, longer exposures are expected. The lower exposure to nitrous oxide in the ED setting may therefore explain the lack of effect seen on the vitamin B_{12} status in ED professionals, whereas reduced vitamin B_{12} levels have been reported in the anesthetic setting.[7–9]

It has to be mentioned that we use only systems with a demand valve and no systems with continuous flow. Such continuous flow systems hazard the consequences of a greater pollution of the room air with concentrations rapidly going above the legally set MAC values.

As a limitation of our study, one could consider the lack of documentation of number and duration of nitrous oxide applications per staff member, precluding an estimate on an individual's exposition to nitrous oxide. Furthermore, we did not record the used nitrous oxide demand valve system (mixture or blender). In addition, the power of this study is limited by the small number of participants, which reduces the power to observe significant effects especially for vitamin B_{12} and MMA, both parameters with a large interindividual variability. However, this study has the advantage that all long-standing staff members of the ED took part except 1 person who refused the written informed consent and one that had to be excluded. Hence, the statement of the study regarding the normal Vitamin B_{12} status of our ED members under regular working conditions is significant.

CONCLUSIONS

Based on our results, there is tentative evidence that the application of nitrous oxide with a demand valve in a pediatric ED has no adverse consequences for the vitamin B_{12} status of the applying personnel.

ACKNOWLEDGMENT

The authors thank the participating staff of the ED and of the PICU.

REFERENCES

1. Annequin D, Carbajal R, Chauvin P, et al. Fixed 50% nitrous oxide oxygen mixture for painful procedures: a French survey. *Pediatrics*. 2000;105:E47.
2. Babl FE, Oakley E, Seaman C, et al. High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation. *Pediatrics*. 2008;121:e528–e532.
3. Collado V, Nicolas E, Faulks D, et al. A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. *Expert Opin Drug Saf*. 2007;6: 559–571.
4. Gall O, Annequin D, Benoit G, et al. Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children. *Lancet*. 2001;358: 1514–1515.
5. Tobias JD. Applications of nitrous oxide for procedural sedation in the pediatric population. *Pediatr Emerg Care*. 2013;29:245–265.
6. Weimann J. Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol*. 2003;17:47–61.
7. Krajewski W, Kucharska M, Pilacik B, et al. Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. *Br J Anaesth*. 2007;99:812–818.
8. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. *Br J Anaesth*. 1987;59:3–13.
9. Irwin MG, Trinh T, Yao C. Occupational exposure to anaesthetic gases: a role for TIVA. *Expert Opin Drug Saf*. 2009;8:473–483.
10. Ekbom K, Lindman N, Marcus C, et al. Health aspects among personnel working with nitrous oxide for procedural pain management in children. *Acta Anaesthesiol Scand*. 2008;52:573–574.
11. Jacques PF, Bostom AG, Williams RR, et al. Relation between folate status, a common mutation in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation*. 1996;93:7–9.